UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

July 8, 2003

MEMORANDUM

SUBJECT: **Chlorpyrifos Methyl:** Status of Toxicity Data Gaps, Impact of New Data on the Risk Assessment and Impact on Cumulative Risk Assessment.
DP Barcode: D291405 PC Code: 059102

TO: Jackie Mosby/Margaret Rice
Special Review and Reregistration Division (7508C)

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THROUGH: Catherine Eiden, Senior Scientist
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At the request of the Special Review and Reregistration Division (SRRD), the Health Effects Division (HED) has reconsidered the toxicity data gaps identified in the chlorpyrifos methyl (CPM) Toxicology Chapter of the RED dated April 19, 2000 to support the continued use of chlorpyrifos methyl on stored grain. Additionally, SRRD has asked HED to comment on the impact of the chlorpyrifos DNT on endpoint selection and safety factors for chlorpyrifos methyl. Finally, HED has been requested to comment on the impact of retaining the use of chlorpyrifos methyl at 6 ppm in stored grain on the Organophosphate Cumulative Risk Assessment.

Data Gaps

HED has addressed the issue of toxicity data gaps in detail in our memorandum entitled "**Chlorpryrifos methyl: Current status of toxicity data gaps and bridging studies from chlorpyrifos**." (John Doherty,7/08/03, TXR #0051734). The findings in that memorandum are summarized briefly here.

At the request of SRRD, HED considered if it were possible to use toxicity data generated on the closely related structural analog, chlorpyrifos (CPY) to address data gaps for CPM. Based on a side-by-side comparison of critical endpoints and available data, the Hazard Identification Assessment Review Committee (HIARC) Co-Chairs concluded that CPM was likely to be less toxic than CPY based on comparison of cholinesterase inhibition, particularly in rats. Given the structural similarity between the two chemicals, toxicity data generated using CPY could be used

to address data gaps for CPM with the exception of the acute toxicity test requirements. Therefore, the only remaining data gaps for CPM are those that remain for CPY and the CPM specific acute toxicity testing data gaps. As CPY toxicity studies are submitted to address remaining CPY data gaps, they can be bridged to CPM.

Additionally, the HIARC Co-Chairs recommended that for risk assessment purposes CPM continue to be regulated using CPM specific endpoints and that the 10X database uncertainty factor for CPM continue to be retained.

CPY DNT Impacts on CPM Regulatory Endpoints and Uncertainty Factors

Endpoint Impacts

As a result of the HIARC's determination that toxicity data for CPY can be used to satisfy data gaps for CPM, SRRD has asked HED to comment on the impact that the CPY developmental neurotoxicity study would have on the risk assessment endpoints and safety factor for CPM.

Regulatory endpoints currently established for chlorpyrifos methyl are based on **chemical specific** toxicity studies. A summary of regulatory endpoints is contained in Table 1, below.

Table 1. Endpoint Selection Summary for CPM

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary General Population Including Infants and Children	NOAEL= 1 mg/kg/day	Inhibition of red blood cell cholinesterase.	CPM Rat developmental toxicity (MRID No.: 44680603)
	UF = 100	**Acute RfD = 0.01 mg/kg/day** **aPAD = Acute RfD/10X DB UF = 0.001 mg/kg/day**	
Chronic Dietary	NOAEL= 0.1 mg/kg/day	Inhibition of plasma cholinesterase.	CPM Chronic/Carcinogenicity feeding study in rats (MRID No.: 42269001)
	UF = 100	**Chronic RfD = 0.001 mg/kg/day** **cPAD = Chronic RfD/10X DB UF = 0.0001 mg/kg/day**	
Dermal Absorption	3% based on comparison of the oral and dermal toxicity studies with chlorpyrifos using a common species and endpoint.		
Short-Term (Dermal/ Inhalation)	Oral NOAEL= 1 mg/kg/day	Inhibition of red blood cell cholinesterase.	See Acute Dietary
Intermediate-Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 mg/kg/day	Inhibition of plasma cholinesterase noted at the 90-day measurement.	See Chronic Dietary
Long Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 mg/kg/day	Inhibition of plasma cholinesterase.	CPM Chronic/Carcinogenicity feeding study in rats (MRID No.: 42269001)

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Carcinogenicity	Classified as "not likely a human carcinogen." Carcinogenicity risk assessment is not appropriate.		

HED has completed the review of the chlorpyrifos developmental neurotoxicity study in rats as well as supplemental data submitted (Sue Makris, Barcodes: D254907, D247891 and D250250). The developmental neurotoxicity study (DNT) in rats is currently classified as guideline-unacceptable pending submission and review of additional morphometric data. In the DNT, a maternal NOAEL was not observed, the maternal LOAEL was <0.3 mg/kg/day (the lowest dose tested) based on plasma and RBC cholinesterase inhibition. Due to lack of morphometric data, an offspring NOAEL and LOAEL could not be determined.

Based on the available comparative toxicological data, the HIARC Co-Chairs (meeting dated ...) determined that CPY is likely a more potent cholinesterase (ChE) inhibitor than CPM. Additionally, work done for the Revised (6/11/2002) Organophosphate Cumulative Risk Assessment (OPCRA) supports these comparative findings. In the cumulative risk assessment CPY was assigned a relative potency factor of 0.06 relative to the index chemical methamidophos, where CPM was assigned a relative potency factor of 0.005 with respect to ChE inhibition. Based on the endpoint (female brain ChE inhibition) used in the Revised OPCRA, CPY is ten times more potent than CPM. Since the regulatory endpoint of concern for CPM is ChE inhibition, based on both the side-by-side comparison of available CPM and CPY toxicity studies with respect to plasma and red blood cell ChE inhibition and on the work on brain cholinesterase inhibition in the OPCRA, it is clear that CPM is a less potent ChE inhibitor, therefore, it is more appropriate to select endpoints from the CPM toxicity studies where ChE inhibition was measured and clear NOAELs were established than to look to the ChE inhibition response in the chlorpyrifos DNT in which clear endpoints for ChE inhibition (NOAELs/LOAELs) were not established.

Therefore, HED concludes that the results of the chlorpyrifos DNT study does not impact the regulatory endpoints of concern for chlorpyrifos methyl.

Safety Factor Impacts

For the purpose of the 2000 CPM RED risk assessment, in the absence of a complete toxicity database with respect to infants and children sensitivity issues, a 10X uncertainty factor was retained for CPM. SRRD has asked HED to revisit this uncertainty factor in light of findings in the CPY DNT and taking into consideration decisions made for CPY.

The HED Hazard Identification Review Committee (HIARC) considered the implications of the CPY DNT results with respect to children's sensitivity and susceptibility on March 28, 2000 (Chlorpyrifos Children's Hazard: Sensitivity and Susceptibility, 3/28/2000, K. Baetcke, V. Dellarco, S. Makris and D. Smegal) for CPY. The HIARC determined that the 10X uncertainty factor (UF) would be retained for CPY based on a complete weight of the evidence approach to sensitivity. Literature data as well as the DNT identified potential brain effects at high doses (well above the doses where ChE inhibition was seen). The neurobehavioral ramifications of these brain effects were unclear, therefore, the 10X UF was retained based on residual concern.

HED has determined that it is appropriate to bridge the results of the CPY DNT to CPM. However, in the absence of a chemical specific CPM DNT study, it is not possible to either establish or to rule out the potential for susceptibility after exposure to CPM based on the weight of the evidence findings for CPY; **therefore, HED will continue to apply a 10X database uncertainty factor to the risk assessment for CPM as a protective measure in the absence of chemical specific DNT data.**

Cumulative Risk Assessment Impact

HED has been asked to run a **screening level** assessment to determine if the inclusion of CPM on stored grain at 6.0 ppm and at 3.0 ppm will have an impact on the cumulative risk assessment. Attachment 1 contains the detailed results of the screening runs. A summary table comparing the findings are shown in Table 2, below.

The conditions of the runs performed by Bill Smith (Chemistry and Exposure Branch, 6/10/03) are summarized as follows:

- **FQPA factors** for OPs were set as in the Revised OPCRA (6/11/02), i.e., methamidophos, dimethoate/omethoate & CPY = 1; all other chemicals = 3.
- CPM was assigned a factor of 10 as a worst case assumption in this **screening level** assessment
- Residues of CPM were exclusively from the Pesticide Data Program (PDP) monitoring data, primarily on wheat which reflects the current 6 ppm use. The PDP data included 1562 samples of wheat with 920 detects/ 642 non-detects, 867 samples of rice with 4 detects/867 non-detects, and 332 samples of oats with 1 detect/331 non-detects.
- Two runs were conducted. The first run duplicated the conditions of the 6/11/02 CRA and did NOT include CPM. The second run reflects addition of CPM. at 6.0 ppm.
- The Point of Departure (POD) for methamidaphos was used to calculate MOEs.

Table 2. Cumulative Run Summary Results (per capita)

	95th Percentile		99th Percentile		99.9th Percentile	
Subpopulations	Without CPM Exposure **MOE**	With CPM Exposure **MOE**	Without CPM Exposure **MOE**	With CPM Exposure **MOE**	Without CPM Exposure **MOE**	With CPM Exposure **MOE**
Children 1 - 2 years	0.000218 **367**	0.000221 **361**	0.000609 **131**	0.000613 **130**	0.001758 **45**	0.001762 **45**
Children 3 - 5 years	0.000174 **459**	0.000178 **449**	0.000492 **162**	0.000496 **161**	0.001520 **52**	0.001524 **52**
Children 6 - 12 years	0.000095 **843**	0.000098 **817**	0.000290 **275**	0.000293 **272**	0.000972 **82**	0.000975 **82**
Youth 13 - 19 years	0.000049 **1618**	0.000051 **1559**	0.000156 **511**	0.000158 **505**	0.000510 **156**	0.000510 **156**
Adults 20 - 49 years	0.000062 **1296**	0.000063 **1267**	0.000186 **431**	0.000187 **427**	0.000630 **126**	0.000631 **126**

Adults 50+ years	0.000070 **1150**	0.000071 **1132**	0.000201 **398**	0.000202 **395**	0.000670 **119**	0.000671 **119**

Results of the screening level runs are consistent with what would be predicted based on the CPM relative potency factor at 0.005 relative to the index chemical, methamidophos, and the low CPM residues which are confined to foods that are not among the most highly consumed on a mg/kg/body weight basis. Based on the results of the runs above using data reflecting the 6 ppm use rate, which showed no significant difference in the OPCRA with or without CPM, no additional runs were completed to reflect lowering on the use rate.

HED concludes that there is no significant impact on the OPCRA as a result of retaining the use of CPM on stored grain at 6.0 ppm.

Attachment 1. Cumulative Risk Assessment Runs

DEEM-FDIC Acute Analysis for Cumulative without CPM

U.S. Environmental Protection Agency Ver. 1.33
DEEM-FCID ACUTE Analysis for CUMULATIVE OP EXPOSURE (1994-98 data)
Residue file: OPCRA-R2.R98 Adjustment factor #2 used.
Analysis Date: 06-09-2003/10:12:57 Residue file dated: 12-17-2002/14:11:03/8
NOEL (Acute) = 0.080000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 1000 MC list in residue file MC seed = 10
Run Comment: "OPCRA-R2: Check sample using same FQPA factors as in OPCRA-R1"

Summary calculations (per capita):

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
Children 1-2 yrs:	0.000218	367	0.000609	131	0.001758	45
Children 3-5 yrs:	0.000174	459	0.000492	162	0.001520	52
Children 6-12 yrs:	0.000095	843	0.000290	275	0.000972	82
Youth 13-19 yrs:	0.000049	1618	0.000156	511	0.000510	156
Adults 20-49 yrs:	0.000062	1296	0.000186	431	0.000630	126
Adults 50+ yrs:	0.000070	1150	0.000201	398	0.000670	119

DEEM-FDIC Acute Analysis for Cumulative with CPM

U.S. Environmental Protection Agency Ver. 1.33
DEEM-FCID ACUTE Analysis for CUMULATIVE OP EXPOSURE (1994-98 data)
Residue file: OPCRA-R2.R98 Adjustment factor #2 used.
Analysis Date: 06-09-2003/11:24:49 Residue file dated: 06-04-2003/12:57:35/8
NOEL (Acute) = 0.080000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 1000 MC list in residue file MC seed = 10

Run Comment: "OPCRA-R2 Check sample using same FQPA factors as in OPCRA-R1, but with chlorpyrifos methyl included [RPF=0.005; FQPA factor = 10X]"

Summary calculations (per capita):

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
Children 1-2 yrs:	0.000221	361	0.000613	130	0.001762	45
Children 3-5 yrs:	0.000178	449	0.000496	161	0.001524	52
Children 6-12 yrs:	0.000098	817	0.000293	272	0.000975	82
Youth 13-19 yrs:	0.000051	1559	0.000158	505	0.000510	156
Adults 20-49 yrs:	0.000063	1267	0.000187	427	0.000631	126
Adults 50+ yrs:	0.000071	1132	0.000202	395	0.000671	119

cc: Donna Davis, John Doherty, Catherine Eiden